Enhanced habit formation in Gilles de la Tourette syndrome

Cécile Delorme, MD[1,2], Alexandre Salvador, MD[3], Romain Valabrègue, PhD[1,4], Emmanuel Roze, MD, PhD[1, 2], Stefano Palminteri, PhD [1,3], Marie Vidailhet, MD[1,2], Sanne de Wit, PhD [5], Trevor Robbins, PhD [6], Andreas Hartmann, MD [1,2,7], Yulia Worbe, MD, PhD, [1,2,7]

1-Sorbonne Universités, UPMC Univ Paris 06, UMR S 975, CNRS UMR 7225, ICM, F-75013, Paris, France

2-Assistance Publique-Hôpitaux de Paris, Department of Neurology, Groupe Hospitalier Pitié-Salpêtrière, 47 boulevard de l'Hôpital, F-75013, Paris, France.

3-Laboratoire des Neurosciences Cognitives, Ecole Normale Supérieure, 29 rue d'Ulm, F-75002, Paris, France

4- Centre de NauroImagerie de Recherche (CENIR), Sorbonne Universités, UPMC Univ Paris 06, UMR S 975, CNRS UMR 7225, ICM, F-75013, Paris, France

5-Department of Psychology, University of Amsterdam, 1018 WB Amsterdam, The Netherlands,

6-Department of Psychology, University of Cambridge, Cambridge, UK

7-French Reference Centre for Gilles de la Tourette Syndrome, Groupe Hospitalier Pitié-Salpêtrière, 47 boulevard de l'Hôpital, F-75013, Paris, France.

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Correspondence to: Dr. Yulia Worbe,
Department of Neurology, Bâtiment Paul Castaigne, Groupe Hospitalier Pitié-Salpêtrière,
47 boulevard de l'Hôpital, 75013, Paris, France.
Email: yworbe@gmail.com

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Abstract

The tics of Gilles de la Tourette syndrome are sometimes described as voluntary movements performed in an automatic or habitual way. Here, we addressed the question of balance between goal-directed and habitual behavioural control in Gilles de la Tourette syndrome, and formally tested the hypothesis of enhanced habit formation in these patients.

To this aim, we administrated a three-stage instrumental learning paradigm to unmedicated and antipsychotic-medicated patients with Gilles de la Tourette syndrome and matched controls. In the first stage of the task, participants learned the stimulus-response-outcome associations. The subsequent outcome devaluation and ”slips-of-action” tests allowed evaluation of the participants' capacity to flexibly adjust their behaviour to changes in action outcomes.

In this task, unmedicated patients relied predominantly on habitual, outcome-insensitive behavioural control. Moreover, in these patients, the engagement in habitual responses correlated with more severe tics. Importantly, the performance of the medicated patients was not significantly different from those of controls or unmedicated patients.

Using diffusion tensor imaging on a subset of patients, we also addressed the question whether the engagement in habitual responding was related to structural connectivity within cortico-striatal networks. Consistent with previous findings, we showed that the engagement in habitual behaviour in Gilles de la Tourette patients correlated with greater structural connectivity within right motor cortico-striatal network. In unmedicated patients, stronger structural connectivity of the supplementary motor cortex with the sensorimotor putamen predicted more severe tics.

Overall, our results indicate enhanced habit formation in unmedicated Gilles de la Tourette patients. Aberrant reinforcement signals to the sensorimotor striatum may be fundamental for

the formation of stimulus-response associations and contribute to the habitual behaviour and tics of this syndrome.

Key words: Gilles de la Tourette syndrome, goal-directed control system, habitual control system, dopamine

Abbreviations used in the text: GTS (Gilles de la Tourette syndrome), GTS_UM (Unmedicated GTS Group), GTS_M (Antipsychotic medicated GTS group), HC (Healthy Controls), FSL (FMRIB Software Library), OCD (Obsessive compulsive disorder), RT (reaction time), YGTSS (Yale Global Tic Severity Scale)

Introduction

Tics, the hallmark of Gilles de la Tourette syndrome (GTS), are brief, recurrent and stereotyped movements or vocalisations (Leckman *et al.*, 2001). Tics are usually perceived as intentional actions (Lang, 1991) triggered by sensory stimuli, so that they could be described as voluntary movements performed in an automatic or habitual way (Singer, 2013; Hallett, 2015).

A balance between flexible and repetitive behaviour, underpinned respectively by goal-directed and habitual neural systems (Everitt and Robbins, 2005; Graybiel, 2008; Balleine and O'Doherty, 2010), is critical for optimal behavioural performance.Disruption of this balance can lead to a wide range of neuropsychiatric disorders (Voon *et al.*, 2014).

Intriguingly, tics and habits share some common features (Leckman and Riddle, 2000; Graybiel, 2008). Habitual behaviours, similarly to tics, are driven by contextual cues through stimulus-response associations. Another important feature of habits is their insensitivity to goal value (Balleine and O'Doherty, 2010). However, this specific feature has not been studied in tics to date.

Dopamine neurotransmission is also crucial for habit formation and tics. For instance, chronic amphetamine administration in rodents led to an acceleration of habit formation, probably via enhanced dopamine neurotransmission (Nelson and Killcross, 2006). In contrast, lesions of the nigro-striatal dopamine pathways or blockade of dopamine neurotransmission via administration of dopamine antagonists disrupted habit formation in rodents (Faure *et al.*, 2005; Nelson and Killcross, 2012).

In GTS patients, PET studies showed abnormalities in tonic-phasic dopamine release (Segura and Strafella, 2013), as well as dopaminergic hyper-innervation and hypersensitivity of dopamine receptors (Buse *et al.*, 2013). In behavioural studies using paradigms of reinforcement learning, which is considered to underlie habitual responses, unmedicated GTS

patients outperformed both controls and GTS patients under dopamine antagonist treatment (Palminteri *et al.*, 2009; Palminteri *et al.*, 2011; Worbe *et al.*, 2011).

Finally, habitual behaviour and tics share some neural substrates as the sensorimotor striatum, which is a part of the sensorimotor cortico-basal ganglia networks, is crucial not only for habit formation (Ashby *et al.*, 2010; Rueda-Orozco and Robbe, 2015), but also belongs to the tic-generator network (Bronfeld *et al.*, 2013).

Here, we addressed the question of balance between goal-directed and habitual behavioural control in GTS, and formally tested the hypothesis of enhanced habit formation in these patients. We also addressed the question of the role of medication with dopamine receptor antagonists, which have been previously suggested to disrupt habit formation.

To this aim, we administrated a three-stage instrumental learning paradigm (de Wit *et al.*, 2007; Worbe *et al.*, 2015b) to unmedicated and medicated GTS patients and controls. The task includes an initial instrumental learning stage, where participants learned stimulus-response-outcome associations on a trial-by-trial basis. In a subsequent outcome-devaluation test, participants had to use their knowledge of the response–outcome associations to direct their choices towards still-valuable outcomes. Finally, in the last task stage, a 'slip-of-action' test, the balance between goal-directed and habitual systems was directly tested as participants were asked to selectively respond to stimuli that signalled the availability of still-valuable outcomes, whereas they were required to withhold responding to stimuli that signalled devalued outcomes. This test was shown to be sufficiently sensitive to evaluate the balance between the two systems in pathological conditions (Gillan *et al.*, 2011) and following pharmacological manipulations (Worbe *et al.*, 2015b).

In a subset of GTS patients included in the study, we also addressed the question of neural correlates of the habitual response, using regression analyses of behavioural performance in

the ‘slip-of-action’ test and cortico-striatal structural connectivity as described previously (de Wit *et al.*, 2012b).

Materials and methods

Participants’ inclusion and exclusion criteria and clinical assessment

The ethics committee approved the study. Inclusion criteria for subjects were age over 18 years, and obtained written informed consent.

Patients were recruited from the GTS Reference Centre in La Pitié-Salpêtrière Hospital in Paris, and were examined by a multidisciplinary team experienced in GTS prior to inclusion into the study. They should have a confirmed diagnosis of GTS fulfilling the Diagnostic and Statistical Manual of Mental Disorders-5 criteria, and medicated patients should be on stable antipsychotic treatment for at least four weeks.

Exclusion criteria were the presence of Axis I psychiatric disorders established by the Mini International Neuropsychiatry Inventory (Sheehan *et al.*, 1998); including current major depressive episodes, current or past diagnosis of psychotic disorder, autistic spectrum disorder, substance abuse aside from nicotine, or a neurologic or movement disorder other than tics. We also excluded the subjects with previous or current diagnosis of Attention Deficit Hyperactivity Disorder. A personal history of tics or any concomitant treatment, except contraceptive pill for women served as additional exclusion criteria for the control group.

All subjects underwent a psychological evaluation including the Beck Depression Inventory (Beck *et al.*, 1996), the Spielberger State-Trait Anxiety Inventory (Spielberger, 1989) and the Barratt Impulsivity Scale (Patton *et al.*, 1995). We used the National Adult Reading Test (Bright *et al.*, 2002) as a proxy measure of verbal intelligence quotient. In GTS patients, the

severity of tics was evaluated using the Yale Global Tic Severity Scale (YGTSS/50) (Leckman *et al.*, 1989).

Instrumental learning task

Each participant performed a three-stage instrumental learning task (de Wit *et al.*, 2007; Worbe *et al.*, 2015b), programmed using Visual Basic 6.0. Computerised and standardized oral instructions were given prior to each stage. Overall, participants were instructed to earn as many points as they could from the task.

Instrumental learning stage

This stage is an instrumental learning paradigm in which the participant learns stimulus-outcome-response associations.

At the onset of each trial, the picture of a closed box with a fruit icon on the front (stimulus) was shown (Fig.1A). The participant was instructed to provide an instrumental response, i.e. pressing a right or a left key. For each stimulus, the correct response was rewarded with points and with the picture of an open box containing another fruit icon (outcome). The incorrect response was associated with a picture of an empty box and no points. Six different stimuli were shown alternatively in a random order. They were associated with six outcomes pictures with a 100% contingency, so that the stimulus determined the response-outcome contingency in a deterministic way. For each stimulus picture, the participant had to figure out, by trial and error, which was the correct response (left or right key press) and the associated outcome.

This stage was self-paced and comprised 10 blocks of 12 trials. Each stimulus was repeated 20 times, in order for all subjects to satisfactory learn the stimulus-response-outcome associations. The outcome measures in this stage were the rate of correct responses and the

mean reaction time (RT) in each block. Learning effect was measured across the 10 blocks. It was decided prior to the study that participants performing under chance level would be excluded from the final analysis.

Outcome-devaluation stage

This stage tests the knowledge of outcome-response associations learned in the first stage.

Outcomes (open boxes with fruit icons) were presented in pairs. In each trial, one of the two outcomes was tagged with a red-cross, indicating that it was devalued and would no longer bring points (Fig.1B). The participant was instructed to press the key associated with the still valuable outcome in the pair. The test comprised 36 trials. The participant did not receive any feedback and was shown the total number of points at the end of the stage. The two outcome measures in this stage were the responses accuracy and mean RT.

'Slip-of-action' stage

This stage directly explores the balance between goal-directed and habitual systems.

At the onset of each block, the six outcomes (open boxes with fruit icons) were shown simultaneously for 10 seconds. The two red-cross tagged outcomes indicated that they were devalued and that responding to associated stimuli would no longer bring points (Fig.1C). Stimuli (closed boxes) were then presented alternatively. The participant was instructed to press a correct key for stimuli associated with still valuable outcomes ('Go' trials) and withhold the response for stimuli associated with devalued outcomes ('No-go' trials).

The stage comprised six blocks (total 144 trials). Each stimulus was repeated four times in each block.

To exclude the possibility that new learning contributed to the performance, the participant did not get any feedback and was shown the cumulative number of points at the end of the

stage. The outcome measures in this stage were the rate of responses associated with valuable and devalued outcomes, responses accuracy, and RT.

This stage is crucial for our hypothesis. Selective responding towards valuable outcomes is indicative of a goal-directed strategy, whereas a high rate of responses to stimuli associated with devalued outcomes indicates predominance of the habitual system.

Baseline stage of response inhibition

This stage is a control 'Go-No go' task, in which the cueing stimuli themselves are devalued (Fig.1D), with the same number of trials and blocks as in the 'slip-of-action' stage. At the onset of each block, the six stimuli (closed boxes) were shown simultaneously for 10 seconds. Two of them were devalued, as indicated by a red cross. The participant was instructed to provide correct key-presses for valuable stimuli ('Go' trials) and not to press any key for devalued stimuli ('No-go' trials). The outcome measures were the rate of responses associated with valuable and devalued stimuli, responses accuracy, and RT.

A high rate of responses for devalued stimuli would indicate deficient response inhibition or working memory deficit. This task controls that excessive responding towards devalued outcomes in the 'slip-of-action' stage is purely related to outcome devaluation insensitivity.

Statistical analysis of behavioural data

Statistical analyses were performed using Statistical Package for Social Science (SPSS) version 22.0 (SPSS Inc. Chicago, IL).

Prior to analysis, all variables were tested for Gaussian distribution (Shapiro-Wilk test, $p>0.05$; with log or square root transformation if appropriate). Outlier data (>3 standard deviations above group mean) were removed from the final analysis.

Behavioural data were analysed using mixed-measures ANOVA with group (controls, medicated and unmedicated GTS patients) as the between-subjects factor and main outcome measures on each task stage as the within-subjects factor. *Post-hoc* analyses were performed usinga Student paired t-test. Responses accuracy and RT were compared using univariate ANOVA.

Demographic data were analysed using two-way ANOVA with group as a between-subjects factor. We used Bonferroni correction for multiple comparisons in all paired and post-hoc tests. We performed a correlation analysis between clinical data and outcome measures of the task using Pearson's correlation coefficient r and Fisher's z-transformation (Benjamini *et al.*, 2001).

Neuroimaging data

Image acquisition

Diffusion Tensor images were acquired using echo planar imaging on a 3T Siemens Trio MRI scanner (body coil excitation, 12-channel receive phased-array head coil). Axial slices were obtained using the following parameters: echo time: 87ms; repetition time: 12s; 65 slices; matrix: 128x128; voxel size: 2x2x2mm; partial Fourier factor: 6/8; grappa factor: 2; read bandwidth: 1502Hz/pixel; flip angle: 9°. Diffusion weighting was performed along 50 directions using a b-value of 1000 sec.mm^{-2}. A reference image with no diffusion weighting was also obtained. Patients were asked to suppress their tics during image acquisition to avoid movement artefacts.

Image processing

FSL (http://fsl.fmrib.ox.ac.uk/) tools were used for all analyses, with a procedure as previously described (de Wit *et al.*, 2012b).

Briefly, images pre-processing included: i) correction for geometric distortion secondary to eddy currents, ii) detection and correction of movement artefacts by comparison with the corresponding null b-value slice and interpolation in the q-space (Dubois *et al.*, 2010), iii) brain-extraction using Brain Extraction Tool, iv) fitting a diffusion tensor model to raw diffusion data. Distribution of diffusion parameters at each voxel was then built-up using the bedpostx toolbox (fibres modelled by voxel = 2, burn in = 1000).

Whole-brain probabilistic tractography was performed from two independent seed regions: the posterior sensorimotor putamen and the anterior caudate nucleus. Seed regions masks were created in each participant's diffusion space. Posterior putamen was anatomically defined as the segment of the putamen caudal to the VCA line of Talairach (vertical line traversing the anterior commissure, perpendicular to the anterior commissure-posterior commissure line). Anterior caudate was defined as the segment of the caudate rostral to the coronal slice containing the interventricular foramina (Fig.2A) (de Wit *et al.*, 2012b). The FSL probtrackx toolbox (5000 samples, curvature threshold 0.2, no waypoint, exclusion or termination masks) builds connectivity distributions between given seed regions and every other voxel in the brain by repetitively sampling from the distributions of principal diffusion directions. This resulted in tractography images in which each voxel was assigned a value depending on the strength of connectivity to the seed region (Fig.2B). All subjects' images were then aligned into Montreal Neurological Institute (MNI) space. Statistical analysis of tractography images was carried out using Tract-Based Spatial Statistics (threshold 0.2) (Smith *et al.*, 2006).

Regression analysis of neuroimaging data

To account for neural substrates of behavioural performance, we performed whole-brain nonparametric cluster-wise statistical testing using FSL randomise, with the rate of responses

towards devalued outcomes in the 'slip-of-action' stage as a behavioural regressor. After voxelwise correlations against the behavioural regressor, FSL randomise assessed the significance of the model fit by comparing each statistic to a null distribution which was generated by randomly shuffling the original dataset 25000 times. Threshold-free-cluster-enhancement (TFCE) was used to increase signals in areas that exhibited spatial clustering (Smith *et al.*, 2006). To protect against false positives, resulting statistical maps were thresholded at $p < 0.001$ with a minimal cluster extent of 10 contiguous voxels. A similar regression analysis was performed using the YGTSS/50 score as a behavioural regressor.

Results

Subjects' characteristics

Twenty subjects were recruited in each group (Unmedicated GTS patients: GTS_UM group, antipsychotic-treated GTS patients: GTS_M group, Healthy controls: HC). Three subjects in each group failed to perform above chance in the instrumental learning stage and were therefore excluded from the final analysis.

Demographic and clinical data are reported in Table 1. All groups were matched for gender, age, and National Adult Reading Test score. Beck Depression Inventory scores were under the cut-off of 8 in all three groups (Mean ± SEM; GTS_UM: 5.647 ± 1.280; GTS_M: 7.647 ± 1.257; HC: 2.059 ± 0.597). Four GTS patients (2 patients in each group) had concomitant obsessive compulsive disorder (OCD) (YBOCS/40, Mean ± SEM: 14.75 ± 2.50).

In the medicated GTS group, twelve patients were under aripiprazole monotherapy, two were treated with pimozide, one with risperidone and two patients had a mixed antipsychotic treatment.

Performance in the instrumental learning task

Instrumental learning stage

As shown in Fig.3A (see also Supplementary Table), all groups of subjects successfully learned the instrumental contingencies from the task (Main effect of learning: $F_{(9,48)} = 59.268$, $p<0.001$), with no difference in the learning rate among groups (Main effect of group: $F_{(2,48)} = 0.084$, $p = 0.920$). In all three groups, the RT decreased across the blocks (Main effect of block: $F_{(9,48)} = 59.430$, $p<0.0001$), with no significant difference among groups (Main effect of group: $F_{(2,48)} = 0.563$, $p = 0.573$).

Mean response accuracy was as follows (Mean ± SEM): GTS_UM: 82.990 ± 2.250; GTS_M: 81.863 ± 2.961; HC: 83.235 ± 2.324, $F_{(2,48)}=0.084$, $p=0.920$.

Outcome devaluation stage

As shown in Fig.3B, there was no difference among groups in response accuracy (Main effect of Group: $F_{(2,48)} = 3.120$, $p = 0.054$) or RT ($F_{(2,48)} = 0.751$, $p = 0.477$) (see Supplementary Table for means and SEM).

'Slip-of-action' stage

There was a main effect of Outcome (valuable or devalued) ($F_{(1,48)} = 51.867$, $p <0.001$), a main effect of Group ($F_{(2,48)} = 3.271$, $p = 0.047$) and a trend towards group X outcome interaction ($F_{(2,432)} = 2.088$, $p = 0.066$).

In paired groups comparisons, a significant difference was found in unmedicated patients compared to controls ($p = 0.041$), as the former exhibited a significantly higher rate of responses towards devalued outcomes in *post hoc* analyses ('No-go' trials, $F_{(2,48)} = 3.928$, $p = 0.027$; Mean ± SEM, GTS_UM: 61.928 ± 34.201; GTS_M: 47.743 ± 32.126; HC: 33.1699 ± 28.336) (Fig. 3C).

There was no significant difference between the medicated GTS patients and controls ($p = 0.533$), or between the two GTS groups ($p = 0.723$). There was no difference in the rate of responses to valuable outcomes ('Go' trials) among groups ($F_{(2,48)} = 0.053$, $p = 0.949$).

No significant difference was found in responses accuracy to stimuli associated with either valuable ($F_{(2,48)} = 0.107$, $p = 0.899$; Mean ± SEM: GTS_UM: 90.904 ± 14.417, GTS_M: 89.750 ± 15.388, HC: 91.998 ± 12.645) or devalued outcomes (Mean ± SEM: GTS_UM: 90.119 ± 3.355, GTS_M: 91.646 ± 3.272, HC: 90.373 ± 3.762).

No significant difference was found in the RT to valuable outcomes ($F_{(2,48)} = 1.486$, $p = 0.236$), but there was a significant difference in the RT to devalued outcomes ($F_{(2,48)} = 3.928$; $p=0.027$; Mean ± SEM: GTS_UM: 1135.296 ± 48.855; GTS_M: 987.370 ± 60.733, HC: 1191.736 ± 48.213). *Post-hoc* analysis showed significantly shorter response times in medicated GTS patients compared with controls ($p = 0.028$).

Baseline test of response inhibition

There was a significant effect of Stimulus (valuable or devalued) ($F_{(2,48)} = 3164.663$, $p <0.001$) and a main effect of Group ($F_{(2,48)} = 3.300$, $p = 0.045$), but no group x stimulus interaction ($F_{(2,48)} = 0.324$, $p = 0.725$). *Post-hoc* comparisons showed no difference among the groups in responses to valuable ($F_{(2,48)} = 0.488$, $p = 0.617$) or devalued stimuli ($F_{(2,48)} = 1.366$, $p = 0.265$) (Fig.3D).

There was no difference in the RT to valuable stimuli ($F_{(2,48)} = 1.092$, $p = 0.344$), but a difference in the response time to devalued stimuli ($F_{(2,48)} = 3.661$, $p = 0.034$). However, *post hoc* tests showed no significant difference ($p = 0.058$) after Bonferroni correction for multiple comparisons. Means are reported in the Supplementary Table.

Regression analysis of behavioural and neuroimaging results

We performed hypothesis-driven correlation analysis of the response rates to devalued outcomes in the 'slip-of-action' stage with severity of tics measured by the YGTSS/50, which showed a positive correlation ($r = 0.414$, $z = 1.647$, $p = 0.049$) (Fig. 4A) in the unmedicated GTS group, but no significant correlation in the medicated GTS group ($r = 0.105$, $z = 0.394$, $p = 0.347$). There was no correlation between the rates of responses to devalued outcomes and scores in the Barratt impulsivity scale ($r = -0.156$, $z = 1.0897$, $p = 0.1379$).

After quality checks for movement artefacts, Diffusion Tensor imaging data on 15 right-handed GTS patients (GTS_UM; n = 10, GTS_M, n = 5) were included in final analysis. The right motor cortex (Fig.4B) showed a significant connectivity to the posterior putamen after regression with the response rate on devalued outcomes in the 'slip-of-action' stage. In the subgroup of unmedicated GTS patients only, a stronger connectivity of the supplementary motor cortex with the posterior putamen predicted the severity of tics measured by YGTSS/50. There were no significant voxels in regression analysis with a caudate ROI.

Discussion

Using an instrumental learning paradigm, we showed that unmedicated GTS patients relied predominantly on habitual, outcome-insensitive behavioural control. Moreover, in these patients, the engagement in habitual response correlated with the severity of tics. Importantly, the performance of the medicated GTS patients was not different from that of controls.

The engagement of GTS patients in habitual behaviour was predicted by a stronger structural connectivity between the right motor cortex and the posterior sensorimotor putamen. In unmedicated GTS patients, a stronger structural connectivity between the supplementary motor cortex and the posterior putamen predicted more severe tics.

Enhanced habit formation in GTS patients

The instrumental learning paradigm has been used to address the balance between habitual and goal-directed behavioural controls in numerous previous studies on healthy controls (de Wit *et al.*, 2007; de Wit *et al.*, 2012c), in pathological conditions such as OCD (Gillan *et al.*, 2011) and autistic spectrum disorders (Geurts and de Wit, 2014) or using pharmacological manipulations (de Wit *et al.*, 2012a; Worbe *et al.*, 2015b).

In particular, the 'slip-of-action' stage has been shown to be sensitive to the balance between the two behavioural systems, with a higher rate of responses towards devalued outcomes indicating a shift to the habitual behavioural control. Indeed, in unmedicated GTS patients, reliance on habitual control in this test was not explained by altered learning of stimulus-outcome-response associations, motor response disinhibition or higher impulsivity scores as indexed respectively by instrumental learning and outcome devaluation stages of the task, baseline test of response inhibition, and Barrat impulsivity scale.

Some of GTS patients had also associated obsessive-compulsive behaviours that were previously shown to disrupt the balance between two behavioural controllers (Gillan *et al.*, 2011). However, in pure OCD without tics, an overreliance on habits resulted from a deficit in goal-directed control due to impaired knowledge of outcome-response association (Gillan *et al.*, 2011). Such outcome-response association learning was intact in both groups of GTS patients as shown in outcome devaluation test. The positive correlation between responses to devalued outcomes and severity of tics in unmedicated GTS would also argue against the contribution of obsessive-compulsive behaviours to present results.

Our results so far suggest that overreliance on habits in unmedicated GTS patients would result from enhanced habit formation rather then impaired goal-directed behavioural control. Indeed, in humans (Tricomi *et al.*, 2009) and other animals (Dickinson, 1985), intensive training reinforce stimulus-response associations, and goal-directed behaviours tend to become more and more habitual over time. In GTS patients, reinforcement of direct,

inflexible stimulus-responses associations could lead to an earlier transfer from goal-directed to habitual behaviours. Dopamine, which provides reinforcement signals to the striatum and facilitates the generation of actions according to previous outcomes (Pessiglione *et al.*, 2006; Schultz, 2013), is known to contribute to motor leaning and habit formation. In unmedicated GTS patients, an enhanced sensitivity to appetitive reinforcement has been shown in associative and motor learning paradigms, and was alleviated by antidopaminergic drugs (Palminteri *et al.*, 2009; Palminteri *et al.*, 2011; Worbe *et al.*, 2011). The aberrant reinforcement signals to the sensorimotor striatum may be fundamental to the formation of stimulus-response associations and contribute to habitual behaviours and tics in GTS.

Role of dopaminergic medication on habit formation in GTS

Reliance on habitual control was a feature of unmedicated GTS patients, while GTS patients under antipsychotic medication did not perform differently in the task compared to healthy controls or unmedicated patients.

Previous rodent studies (Nelson and Killcross, 2012) suggested that dopamine antagonists could shift the balance between the two behavioural systems towards goal-directed performance. Our results do not fully corroborate the conclusions of this study. However, the antipsychotic drug we used, as most of the GTS patients were treated by aripiprazole, dopamine D2-receptors partial agonist, could influence our results. A recent PET study suggested that aripiprazole could increase or decrease the dopamine synthesis depending on the baseline dopamine levels, acting rather as a dopamine stabiliser (Ito *et al.*, 2012) than as a classic dopamine antagonist. This particular pharmacological profile could result in partial effect on reinforcement leaning and habit formation mechanisms. For instance, contrary to classic dopaminergic antagonists, our previous study in GTS patients showed that aripiprazole did not reduce reward sensitivity (Worbe *et al.*, 2011).

Motor cortico-striatal network underpin the habitual control in GTS patients

Habitual and goal-directed behaviours are underpinned by distinct cortico-basal ganglia networks. The goal-directed system is supported by the ventromedial prefrontal cortex and the ventral striatum (Everitt and Robbins, 2005; Dolan and Dayan, 2013), whereas habitual behaviours were linked to the activity of the dorsolateral striatum (Tricomi *et al.*, 2009; Lee *et al.*, 2014).

A previous study using the same instrumental task and probabilistic tractography in healthy volunteers (de Wit *et al.*, 2012c), showed that engagement in goal-directed behaviour correlated with increased connectivity between the caudate nucleus and the ventromedial prefrontal cortex, whereas a tendency to provide habitual responses correlated with connectivity between posterior putamen and premotor cortex.

Here, we used a previously described neuroimaging method (de Wit *et al.*, 2012c) on a subset of GTS patients to address the question whether the engagement in habitual response was related to structural connectivity within cortico-striatal networks. Consistent with a previous result, we showed that in GTS patients the engagement in habitual behaviour correlated with higher structural connectivity within right motor cortico-striatal network. Moreover, a stronger structural connectivity of supplementary motor cortex with sensorimotor putamen predicted more severe tics, which is also in line with our previous results (Worbe *et al.*, 2015a).

Overall, our data suggest that higher structural connectivity within premotor and motor cortico-striatal networks support both more severe tics and a stronger engagement in habitual response. Noteworthy, one recent study showed that habit reversal therapy in GTS patients, which notably reduces the severity and number of tics, resulted in a change of activity of cortico-basal ganglia network by decreasing putaminal activation (Deckersbach *et al.*, 2014).

Study limitations

Our study has some limitations. The first limitation is a small number of patients included in the neuroimaging part of the study, which limits the statistical power. Even if the results did not survive the whole brain correction for multiple comparisons, the use of a lower threshold of statistical significance and a minimum cluster size limited the risk of false positives. Moreover, our results are consistent with previous data.

The second limitation is the population of GTS patients that we used in this study. We focused on adult patients with GTS, that usually have a stable clinical phenotype (McGuire *et al.*, 2013). Therefore, we cannot exclude that compensatory mechanisms for tics influenced our results. Further studies on GTS children are needed to support our conclusions.

Finally, although our behavioural findings are significant and consistent with current knowledge about GTS, they probably cannot account entirely for the complexity of tic genesis and persistence.

Conclusions

Unmedicated GTS patients showed enhanced habitual response in the instrumental learning task, which also positively correlated with the severity of tics. The engagement in habitual response was underpinned by a higher structural connectivity within motor cortico-striatal network and likely resulted from the hyperactivity of the dopaminergic system in GTS.

Figure Legends

Figure 1. Task description. A. Instrumental learning stage. In this example, in two different trials, participants are presented with a strawberry or a lemon on the outside of a box (Stimuli). For each of the trials, if the correct key is pressed (R – Right for strawberry and L – left for lemon), participants are rewarded with another fruit (Outcome) on the inside of the box and points. If the incorrect key is pressed, an empty box is shown and no points are earned. **B. Outcome-devaluation stage:** The participant is instructed to press the key that brought the still-valuable outcome (the one which is not red-crossed) in the first stage. In this example, the subject should press the left key, as it was previously associated with the coconut picture. **C. Slips-of-action test.** In this example, the initial screen indicates that the banana and the coconut outcomes are no longer valuable. The participant is then presented with a succession of stimulus pictures. He should press the correct key (right) to the strawberry stimulus, but withhold his response to the lemon stimulus (which was associated with the devalued coconut). **D. Baseline test of response inhibition.** In this example, the initial screen indicates that the strawberry and kiwi stimuli are devalued. The participant is then presented with a succession of stimulus pictures. He should press the correct key (left) to the lemon stimulus, but withhold his response to the strawberry which is a devalued stimulus.

Figure 2. Regions of interest-seeded tractography. A. Masks of the anterior caudate (green) and posterior putamen (red). **B.** Tractography images seeded from the anterior caudate. **C.** Tractography images seeded from the posterior putamen. Coordinates are shown in MNI.

Figure 3. Results of behavioural task. A. Instrumental learning stage. **B.** Outcome-devaluation stage. **C.** 'Slip-of action' stage. D) Baseline stage. Error bars represent SEM. *: $p < 0.05$

Figure 4. Correlation and regression analysis. A. Cortical cluster showing the connectivity from the posterior putamen, after regression with the rate of responses towards devalued outcomes ($p < 0.001$); voxels = 16, peak coordinates: x = 80, y = 93, z = 126. Neurological convention (right is right) and MNI coordinates are used. **B.** Correlation between the rates of responses associated with devalued outcomes in the 'slip-of-action' stage and the YGTSS/50, in the two GTS groups.

Table 1. Demographic data of subjects included in the study

	HC (n=17)	GTS_UM (n=17)	GTS_M (n=17)	F	p
Age	29.588 ± 2.854	32.823 ±3.203	29.294±2.601	0.457	0.636
Gender (F/M)	8/9	5/12	5/12	1.545 (a)	0.462
YGTSS/100	NA	36.471±4.160	35.353±3.686	0.201 (b)	0.842
YGTSS/50	NA	18.177±2.503	17.706±1.771	0.153 (b)	0.879
NART	300.235 ± 23.094	269.353 ± 23.570	270.571±24.873	0.557	0.577
STAI (trait)	47.941 ± 0.864	46.529 ± 0.625	47.765±0.957	0.865	0.428
STAI (state)	47.857 ± 1.213	50.312 ± 1.781	49.574±1.436	0.68	0.512
BIS Total	59.941 ± 2.276	64.235±2.970	69.000±2.818	2.808	0.07

HC: healthy controls ; GTS_UM: unmedicated GTS patients ; GTS_M: medicated GTS patients ; YGTSS: Yale global tic severity scale ; NART: National adult reading test. STAI : State-trait anxiety inventory, BIS : Barrat impulsivity scale. Reported as Mean ± SEM. (a): χ 2 test. (b): two samples t-test.

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